REMARKS/ARGUMENTS

The claims in the present application were previously allowed in an office action, dated May 4, 2006, subject to cancellation non-elected claim 9. Applicant responded to the May 4, 2006, office action by cancelling claim 9. To it's surprise, Applicant received the present office action, dated September 12, 2006, which raises new grounds of rejection of claims 14-30 under 35 U.S.C. §101, as being directed to non-statutory algorithm type subject matter, and under 35 U.S.C. §102(b), as being anticipated by Yager et al. For the reasons explained below, Applicant respectfully submits that the grounds of rejection are without merit and should be withdrawn.

Summary of Invention

The claims in this application are generally directed to a method for aligning a plurality of nucleotide sequence data traces that are indicative of the positions of a plurality of nucleic acid base types in a target nucleic acid sequence. As explained in the specification, and as is well-known to those in the art of nucleotide sequencing, a data trace is a graphical representation of multiple nucleotide polymer fragments (polynucleotides) of different lengths separated on the basis of molecular weight. An example of a data trace is shown in Figure 7 of the specification. Figure 7 shows a typical data trace having a series of "peaks," each of which represent a discreet polynucleotide fragment. Importantly, the data trace of Figure 7 is actually a synthesis of four separate data traces, each of which represent an independently generated data trace of polynucleotide fragments ending with one of four different base types – A, G, C or T – found in nucleotide polymers. In some methods, four separate data traces of each of the different base types are first generated, and the four separate data traces are then overlaid such that peaks of one data trace are located in the correct position relative to the molecular weight of neighboring peaks in the other data traces. By correctly aligning the plurality of data traces, a complete nucleotide sequence of a target nucleotide can be generated that combines the termination fragments of all base types A, G, C and T. This process is commonly referred to as "*base-calling,*" and essentially involves assigning a nucleotide base to a given position within the nucleotide sequence in order to establish the correct order of nucleic acid base signals of one data trace relative to the other data traces.

The present invention relates to a method of base-calling. Base-calling is complicated by the fact that the distances between peaks is not always constant, nor is the peak height or peak width always constant. In accordance with the methods of the present invention (as recited in the

four independent claims 14, 18, 19 and 20), one or more of the separate data traces of the four different base types – A, G, C or T – are combined and aligned by (1) selecting peaks of highly conserved internal bases that function as an alignment point, (2) assigning a reference position number to the alignment point, (3) assigning a sequence position number to each peak in each of the plurality of data traces that maximizes the number of times that the sequence position number and the reference position number are assigned to a base of the same type, and then (4) aligning the data traces based on the assigned sequence position numbers. Essentially, the claimed method fixes the position of highly conserved nucleotide bases within the sequence and then uses those fixed positions as a reference point to establish the position of bases within the sequence. Claims 18, 19 and 20 differ from claim 14 in that, among other things, they further recite use of the average peak spacing interval between the alignment points as a means of assigning peak position numbers.

As explained below, the invention, *as set forth in the claims*, constitutes patentable subject matter and is distinguishable over the cited prior art.

Rejection Under 35 U.S.C. §101

The office action rejects claims 14-30 under 35 U.S.C. §101, as being directed to non-statutory algorithm type subject matter. More particularly, the office action states that "the claimed method does not result in any physical transformation or produce any tangible, concrete, and useful results." Applicant respectfully disagrees for the following reasons.

MPEP 2106 specifically provides that a claim satisfies the requirement of a statutory process if it manipulates data *representing physical objects or activities*. In the present case, the claims are directed to a method "for alignment of a plurality of data traces indicative of the positions of a plurality of nucleic acid base types in a target nucleic acid sequence." In this claim, the data (the "data trace") is an intangible representation of an actual physical property, "nucleic acid bases" and their relative molecular weight. The transformation occurs when the "nucleic acid base" is detected and an electrical signal is produced, resulting in a peak that is then represented in "data trace." The peaks of the data base do not represent arbitrary abstract data – they represent actual physical entities (polynucleotide fragments) having particular physical properties (molecular weight and terminal base type). For example, claim 1 recites steps of selecting "alignment points *corresponding to an internal peak associated with internal bases* that are highly conserved", as well as "alignment points selected from the group consisting of a

primer peak *associated with unextended primer*, a full-length peak *associated with full length product* produced during a cyclic primer extension reaction with two primers." The data of the claimed process thus "represents physical objects and activities," as required by MPEP 2106. The process of the claimed invention manipulates that data in a specified manner, to combine the individual data traces and generate a complete DNA sequence. As specifically recited by the claim language, this process has real world value in that proper alignment of the individual data traces for each of the nucleic acid base types results in an accurate nucleic acid sequence of a strand of DNA, which is in fact a tangible, concrete, and highly useful result. Indeed, the success and future of the entire genetic testing industry is predicated accurate sequencing of DNA! Because the rejection is based on an incorrect construction of the claims (and incorrectly presumes that the data manipulated in the claimed process does not represent physical objects or activities), Applicant submits that the grounds of rejection are improper and should be withdrawn.

The office action more particularly states that claims 14-30 are rejected "because the claimed method does not result in any *physical transformation* or produce any tangible, concrete, and useful results." This statement, however, misstates the rule articulated in MPEP 2106, which requires that the process "manipulate data *representing physical objects or activities*"; MPEP 2106 does <u>not</u> require that the process "result in any physical transformation" *per se*. Because the office action relies on a misstatement of the requirement of a statutory algorithm process, Applicant requests that the rejection be withdrawn and the claims allowed.

MPEP 2106 further provides that even "if a claim does not clearly fall into one or both of the safe harbors, the claim may still be statutory if it is *limited to a practical application in the technological arts*." In the present case, the claims recite steps directed to a process (which is typically performed by a computer) that constitutes a "practical application in the technological arts." The claimed process for "alignment of a plurality of data traces indicative of the positions of a plurality of nucleic acid base types in a target nucleic acid sequence" results in a more accurate DNA sequence, which can be used to more accurately identify genetic mutations and provide more accurate and useful clinical analysis of genetic diseases of a patient. Applicant submits that this constitutes a "practical application in the technological arts." Again, in view of the fact that the claimed process results in a highly valuable practical application in the DNA

sequencing arts, Applicant submits that the claimed process further satisfies the requirement of statutory algorithm process subject matter, as set forth in MPEP 2106.

Rejections Under 35 U.S.C. §102(b)

The office action also rejects claims 14-30 under 35 U.S.C. §102(b), as being anticipated by Yager et al. The office action states that Yager et al. discloses "a method for alignment of a plurality of data traces indicative of the positions of a plurality of nucleic acid base types in a target nucleic acid sequence." This statement is not, however, a factually accurate characterization of Yager et al.

Yager et al. does not describe a method for "alignment" of a plurality of data traces. Yager et al. describes a DNA sequencing and genotyping method that simultaneously amplifies and generates sequencing fragments using RT-PCR followed by CLIP sequencing. Although Yager et al. discusses processing of raw sequence data and data traces, no mention is made of any particular methodology for aligning data traces for each of the four A, C, G and T nucleic acid base types. More particularly, the citations to Yager et al. in the office action relate to processes applied to *already completed* DNA sequences (i.e., the data traces have already been aligned), and not to processes for *aligning* partial data traces which result in completed DNA sequences. The following table illustrates the specific differences between the elements of the claimed invention and the disclosure of Yager et al.:

Claimed invention (claim 1)	Yager et al. (citation in office action)
A method for alignment of a plurality of data traces indicative of the positions of a plurality of nucleic acid base types in a target nucleic acid sequence, comprising the steps of:	(Abstract) No disclosure of any "alignment" methodology.
(a) selecting for each data trace one or more alignment points corresponding to an internal peak associated with internal bases that are highly conserved in the target nucleic acid, and	(page 1294, Figure 11, and page 1295, Figure 12) Figure 11 shows a complete DNA sequence, as evidenced by all four base types A, C, G and T. Figure 11 does not disclose selection of "one or more alignment points," or selection of "internal peak associated with internal bases that are highly conserved."

Claimed invention (claim 1)	Yager et al. (citation in office action)
	Figure 12 also shows only <u>complete</u> DNA sequences, as evidence by the presence of all four base types in each data trace. Figure 12 also does not disclose selection of "one or more alignment points," or selection of "internal peak associated with internal bases that are highly conserved."
further selecting alignment points selected from the group consisting of a primer peak associated with unextended primer, a full-length peak associated with full length product produced during a cyclic primer extension reaction with two primers, and assigning to each alignment point a reference position number reflecting the relative position of the alignment point with respect to the sequence as a whole;	(Section 4.5.3, from page 1294, column 2, to page 1295, column 2, line 13) Section 4.5.3 discloses methods for "genotyping at low heterozygosity levels" and teaches that "[b]ase calling and sequence comparison was performed automatically, using the GeneObjects software." This teaching does not teach the claimed method of base-calling, which requires "selecting alignment points" from among the group of "primer peak associated with unextended primer," "a full-length peak associated with full length product" or "assigning to each alignment point a reference position number." The mere recitation of the words "base calling" does <u>not</u> therefore teach the limitations of the claimed invention.
(b) assigning a sequence position number to each peak in each of the plurality of data traces that maximizes the number of times that the sequence position number and the reference position number are assigned to a base of the same type; and	(page 1295, Figure 12 A-F) Again, Figure 12 shows only <u>complete</u> DNA sequences, as evidence by the presence of all four base types in each data trace. Figure 12 also does not disclose "assigning a sequence position number to each peak in each of the plurality of data traces that maximizes the number of times that the sequence position number and the reference position number are assigned to a base of the same type."
(c) aligning the data traces based on the assigned sequence position numbers.	Yager et al. does not teach "aligning the data traced based on the assigned sequence position numbers."

With regard to the rejection of claims 15-17 and 22-30, paragraph 10 of the office action states that Yager discloses "heterogeneous multiplets and four data traces, one for each nucleotide based [sic] type (page 1293, Figure 10, page 1294, Figure 11, and page 1295, Figure 12)." This ground of rejection, however, improperly ignores limitations of claims 15-17 and 22-30, which must be considered in determining the differences between the claimed invention and the prior art, as explained below.

Specifically, claim 15, which depends from claim 14, further recites the limitation that "*at least some* of the *internal peak alignment points* are members of heterogeneous multiplets." Claim 16, which also depends from claim 14, further recites the limitation that "*all* of the *internal peak alignment points* are members of heterogeneous multiplets." Although Yager obviously shows that the nucleotide sequences are grouped in "multiplets" (as are all nucleotide sequences), Yager does not, however, teach that any of the multiplets are used as "internal peak alignment points." Yager also does not teach that "at least some" or "all" of the internal peak alignment points are multiplets. Yager does not, therefore, teach all the limitations of claims 15 or 16. Furthermore, because claims 15 and 16 depend from claim 14, which is patentably distinguishable over Yager et al., claims 15 and 16 are also patentable.

Claim 17, which also depends from claim 14, further recites that "four data traces, one for each nucleotide base type, are aligned." Because claim 17 depends from claim 14, which is patentably distinguishable over Yager et al., for the reasons described above, claim 17 is also patentable.

Finally, in paragraph 11, the office action states that claims 18-21, which recite the step of determining "average peak spacing interval," are anticipated because Yager discloses "a set of five or more alignment points" (page 1290, column 1, section 4.2.3, especially, at least "20 points per peak must be collected in order to record the peak shape accurately.") Again, the rejection is based on an incorrect understanding of the teaching of the prior art and resultant misapplication to the claimed invention, for the following reasons.

In section 4.2.3 (at page 1920, column 1), Yager does not teach the use of "average peak spacing interval." Indeed, by stating that Yager teaches "average peak spacing interval," the office action misrepresents that Yager et al. actually uses the phrase "average peak spacing interval." Applicant, however, can find no such teaching in Yager, and the office action points to no column or line where such a teaching is found. In the absence of such a teaching, it is

improper for the office action to suggest that such a teaching is present, and even more improper to suggest that such a teaching is present by "quoting" exact phraseology that is not present. To the contrary, Yager teaches that accurate base calling requires that "peak shapes must be accurately recorded" and states that each peak requires that digital sampling of the "analog fluorescence signal" of "≥20 points per peak must be collected" (emphasis added). This statement, however, relates to the sampling frequency of the fluorescent signal generated by a single labeled nucleotide fragment representing a *single* peak in a data trace, and has no relevance whatsoever to the use of *multiple* peaks as *alignment points*.

Paragraph 11 further states that Yager discloses "average peak spacing" (page 1284, Figure 2, page 1285, column 1, section 3.3.1, to page 1286, line 5). Nothing within the cited portions of Yager, however, teach anything about "average peak spacing." The cited section of Yager encompasses materials on 3 different pages of Yager, but fails to point to any specific language within these three pages that teaches any element of the claimed invention. To the extent that the patent office continues to rely on this ground of rejection, Applicant demands that any subsequent office action identify with particularly the specific language of the prior art that is being relied upon in support of the rejection.

The above grounds of rejection being relied upon are based on a misunderstanding and misapplication of the prior art. The office action has misconstrued the prior art and attempted to apply prior art that is completely irrelevant to the claimed invention, not only with respect to particular details, but also with respect to the general objectives of the claimed process. While the claimed invention relates to alignment of multiple *incomplete* data traces (each of which represents a *partial* nucleotide sequence and positions of one of the individual terminal bases), the office action relies on prior art that discloses only general concepts relevant to *complete* data traces that have already been aligned and include *all four* nucleotide bases! The office action further searches for individual words in the claimed invention, and then relies on completely irrelevant teachings in the prior art that use similar terminology but have nothing to do with the invention as a whole. Further still, the office action has ignored limitations recited in the claimed invention, and has failed to establish that each and every such limitation of the claimed invention is present in the prior art. In short, the grounds of the present office action are manifestly based on hindsight reconstruction of the claimed invention. In view of the differences between the

claimed invention and the Yager et al. reference, Yager et al. does not teach each and every element of the claimed invention. Applicant therefore request that this rejection be withdrawn.

In summary, Applicant submits that the claimed invention recites processes that "manipulate data representing physical objects or activities" and "is limited to a practical application in the technological arts." Applicant further submits that the prior art relied upon in the office action is not only irrelevant to the claimed invention, but fails to teach or suggest the claimed elements of the invention. In view of the above amendments and remarks, Applicant respectfully requests that the rejections be withdrawn and the claims allowed.

Respectfully submitted,
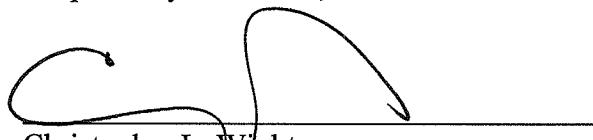
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